(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 1 033 991 B1

(12) **EUROPEAN PATENT SPECIFICATION**

(45) Date of publication and mention of the grant of the patent:
17.04.2002 Bulletin 2002/16

(21) Application number: **98950781.9**

(22) Date of filing: **06.10.1998**

(51) Int Cl.[7]: **A61K 31/58**, A61K 9/12, A61K 9/72, A61P 11/00

(86) International application number:
PCT/US98/20480

(87) International publication number:
WO 99/18971 (22.04.1999 Gazette 1999/16)

(54) MOMETASONE FUROATE SUSPENSIONS FOR NEBULIZATION

MOMETASONFUROAT-SUSPENSIONEN ZUM ZERSTÄUBEN

SUSPENSIONS DE MOMETASONE FUROATE POUR LA NEBULISATION

(84) Designated Contracting States:
AT BE CH DE DK ES FI FR GB GR IE IT LI LU NL PT SE
Designated Extension States:
LT LV RO

(30) Priority: **09.10.1997 US 948118**

(43) Date of publication of application:
13.09.2000 Bulletin 2000/37

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(56) References cited:
EP-A- 0 653 205
WO-A-92/04365
WO-A-95/20393

Remarks:
The file contains technical information submitted after the application was filed and not included in this specification

EP 1 033 991 B1

Printed by Jouve, 75001 PARIS (FR)

Description

INTRODUCTION TO THE INVENTION

[0001] The present invention relates to aqueous suspensions of water-insoluble pharmaceutical substances, and more particularly to suspensions of substances intended for inhalation therapy.

[0002] Use of inhaled therapeutic substances has become common for the treatment of airway disorders, such disorders including, without limitation thereto, asthma, infections, emphysema and various inflammatory conditions. Substances commonly delivered to the lower airway surfaces, that is, the trachea. bronchial tree and lungs, by oral or nasal inhalation include bronchodilators, corticosteroids, anti-infectives and anti-inflammatory medicaments. Various methods have been used for such delivery, including pressurized metered dose inhalers, dry powder inhalers and nebulizers.

[0003] Nebulizers are considered to be instruments generating very fine particles of a liquid in a gas. As is very well known, particles intended for treatment of the lower airway, i.e., the bronchial tree or the lungs, will generally be less than 10 micrometers in the largest dimension, to prevent unwanted deposition onto surfaces of the mouth and pharynx, and more preferably will be less than 5 μm. In addition, particles much smaller than about 0.5 μm in the largest dimension frequently are not easily deposited at the desired location, and a large fraction of these simply will be exhaled by a patient. For these reasons, it is generally desired to produce particles which average 1-7 μm in their largest dimension, while preferably minimizing production of particles having sizes either less than about 0.5 or greater than about 10 μm. The more preferred average particle sizes are in the range of 0.5-5 μm.

[0004] Nebulization, although used more infrequently than other drug delivery techniques, has certain advantages for special patient groups, such as young children and the very infirm. Although somewhat cumbersome equipment is needed and there may be more stringent cleaning requirements than exist for some of the more popular delivery techniques, no particular patient skill or coordination is required: the patient merely needs to breathe normally to introduce the medication into the airway. Thus, treatment can be delivered even to an unconscious patient or an infant. It is also considered an advantage of nebulizers that quantities of moisture are delivered to the airway; this may help to fluidize secretions and tends to increase patient comfort.

[0005] The typical nebulized medication is a water-soluble substance which can form relatively dilute aqueous solutions. This is desired, due to the relatively large volumes of solution which will be entrained in an inhaled air stream, and to the very small quantities of drug which will typically be delivered in a single treatment. Handling of a drug solution is quite uncomplicated: a desired volume of a solution (usually aqueous) is either nebulized directly or is measured into larger volume of sterile water for nebulization.

[0006] However, some very useful inhalation drugs have little or essentially no water solubility. Examples of such drugs are corticosteroids, typically administered in the treatment of asthma by inhalation from pressurized metered dose inhalers, either in alcohol solution or as suspended micronized particles, or from dry powder inhalers of various types.

[0007] It is also known to form an aqueous suspension of drug particles, for nebulization. Commercial products, which have not been made available in all countries, currently include beclomethasone dipropionate (sold by Glaxo under the trade name BECOTIDE) and budesonide (formulated with a citrate-citric acid buffer and Polysorbate 80 surfactant, and sold by Astra under the trade name PULMICORT). Corticosteroids have also been formulated in liposome suspensions in aqueous media, for nebulizer delivery, as in United States Patent 5,192,528.

[0008] The therapeutic advantages of the corticosteroid mometasone furoate for treating disorders of the tower airway make this drug a desirable candidate for delivery by nebulization. Since this drug is not soluble in aqueous media, it has become necessary to develop aqueous suspensions for nebulization.

SUMMARY OF THE INVENTION

[0009] The invention comprises an aqueous suspension of micronized mometasone furoate monohydrate, also containing a nonionic surfactant sodium chloride or potassium chloride, and optionally a pH buffer. Preferred surfactants are those known as polysorbates. The soluble salt may be sodium chloride, in amounts needed to render the solution phase isotonic. When the buffer is present, it preferably will be chosen to maintain a solution pH between about 3 and about 7.

BRIEF DESCRIPTION OF THE DRAWING

[0010] Fig. 1 is a graphical representation of results from the experiment of Example 3.

DETAILED DESCRIPTION OF THE INVENTION

[0011] Percentages expressed herein are meant to indicate percent by weight, unless the context clearly dictates otherwise.

[0012] The suspension formulations of the invention may be delivered to a patient using any of the usual nebulizer devices. Typical commercial nebulizer devices produce dispersions of droplets in gas streams by one of two methods. Jet nebulizers use a compressed air supply to draw up a fluid by venturi action and introduce it into a flowing gas stream, after which the fluid is caused to impact one or more stationary baffles to remove excessively large droplets. Ultrasonic nebulizers

use an electrically driven transducer to subject a fluid to high-frequency oscillations, producing a cloud of droplets which can be entrained in a moving gas stream; these devices are less preferred for delivering suspensions. There are hand-held nebulizers which atomize the fluid with a squeeze bulb air supply, but the more widely used equipment incorporates an electrically powered compressor or connects to a cylinder of compressed gas. Although the various devices which are commercially available vary considerably in their delivery efficiency for a given medicament, they all are useful for the treatment of the present invention; it is necessary for the prescriber to specify an exact amount of medicament formulation which is to be charged to each particular device, since their respective outputs of respirable droplets are far from identical.

[0013] Suspension formulations suitable for nebulization must, of course, contain solid particles of a respirable size (e.g., preferably averaging less than about 5 μm in the largest dimension and more preferably averaging less than about 2 μm) and must maintain their suspended particle size distribution during storage. In addition, the particle-containing droplets formed during nebulization of the formulations must have appropriate sizes for deposition in the desired area of the respiratory system.

[0014] Since the formulations of the invention are to be inhaled, it is necessary that they be free of pathogenic organisms. Thus, they may be prepared and handled under sterile conditions, or may be sterilized before or after packaging. In addition, or in lieu of sterilization, a preservative may be incorporated to minimize the possibility of microbial contamination. In addition, all components of the formulations must be chosen for inhalation safety, as the treated tissues are quite sensitive to irritants; it is commonly known that many of the common preservatives have a considerable potential for causing irritation.

[0015] The inventive formulations comprise water, mometasone furoate monohydrate, a nonionic surfactant, sodium chloride or potassium chloride and optionally a pH buffer.

[0016] Water for use in the formulations should meet or exceed the applicable regulatory requirements for use in inhaled drugs. Specifications established by the *United States Pharmacopoeia* for "Sterile Water for Injection" or "Sterile Water for Inhalation" are examples of water suitable for use to prepare formulations of the invention.

[0017] Mometasone furoate is a corticosteroid having the chemical name 9α,21-Dichloro-11β,17-dihydroxy-16α-methylpregna-1,4-diene-3,20-dione 17-(2-furoate), and is currently marketed by Schering Corporation in cream and lotion formulations for the treatment of dermatologic conditions. Information concerning the preparation and properties of mometasone furoate is given in United States Patent 4,472,393. This compound may be used to prepare mometasone furoate monohydrate for use in the present invention. Information concerning the preparation and properties of mometasone furoate monohydrate is given in PCT International Application WO 92/04365.

[0018] In general, the concentration of mometasone furoate included in the suspension formulation will depend upon the dose to be delivered to the patient, ease of handling and the characteristics of the nebulizer equipment, as the devices vary considerably in their suspension capacities and nebulization efficiencies. Typical suspensions may contain as much as about 5 mg/mL of mometasone furoate, although lower concentrations, such as 50 μg/mL to 1 mg/mL are more customary for most equipment.

[0019] Surfactants are frequently categorized by their chemical nature, i.e., as cationic, anionic or nonionic. Cationic surfactants, such as cetyl pyridinium chloride, and anionic surfactants, such as docusate sodium, do not appear to provide proper dispersions of particles in the formulations.

[0020] Many nonionic surfactants are suitable for maintaining the particulate suspensions of the invention. These include surfactants identified as "polysorbates" in the *CTFA International Cosmetic Ingredient Dictionary*; such surfactants are mixtures of fatty acid esters (predominately monoesters) of sorbitol and sorbitol anhydrides, condensed with ethylene oxide. Although these surfactants vary widely in their hydrophilic-lipophilic balance ("HLB") numbers, they all appear to function well in the invention.

[0021] Commercially available polysorbates which are useful in the invention include those listed in the following table, which shows the CTFA designation (Polysorbate number), identity of the fatty acid used to produce the material and the number of moles of ethylene oxide reacted with each mole of ester. Compositions identified with an asterisk are predominately triesters.

Polysorbate	Acid	Moles EtO
20	Lauric	20
21	Lauric	4
40	Palmitic	20
60	Stearic	20
61	Stearic	4
65*	Stearic	20
80	Oleic	20
81	Oleic	5
85*	Oleic	20

[0022] In general, Polysorbate surfactants will be present in a formulation at about 50 to 500 μg/mL. When the surfactant concentration is below about 20 μg/mL, the particles tend to form cakes which are not easily redispersed.

[0023] Useful surfactants also include the "Poloxamers," which are block polymers of polyoxyethylene and

polyoxypropylene, generally corresponding to the following formula:

$$HO(CH_2CH_2O)_x\,[CH(CH_3)CH_2O]_y\,(CH_2CH_2O)_zH$$

Representative commercially available poloxamer surfactants are listed in the following table, wherein the CTFA designation (Poloxamer number) and average values of x, y and z are given.

Poloxamer	x	y	z
101	2	16	2
105	11	16	11
108	46	16	46
122	5	21	5
123	7	21	7
124	11	21	11
181	3	30	3
182	8	30	8
183	10	30	10
184	13	30	13
185	19	30	19
188	75	30	75
212	8	35	8
215	24	35	24
217	52	35	52
231	6	39	6
234	22	39	22
235	27	39	27
237	62	39	62
238	97	39	97
282	10	47	10
284	21	47	21
288	122	47	122
331	7	54	7
333	20	54	20
334	31	54	31
335	38	54	38
338	128	54	128
401	6	67	6
402	13	67	13
403	21	67	21
407	98	67	98

[0024] Poloxamer surfactants are used at concentrations similar to those for the Polysorbates, although certain members are useful at concentrations up to about 1 mg/mL.

[0025] In general, the chosen surfactant should not materially increase the viscosity of the suspension formulation, since the efficiency of the nebulization process is particularly sensitive to viscosity. Many nonionic surfactants are useful for preparing inhalation and/or injectable drug formulations, and any of these should be suitable for use in the present invention.

[0026] The formulations further include sodium chloride or potassium chloride. This salt performs at least two functions: it minimizes the effects of the inhaled formulation on the normal cell fluid balance of airway cells and also stabilizes the suspension of medicament. For the first function, it is preferred to use sufficient salt concentrations to render the formulation isotonic. It has been found that adequate suspension stability is produced by isotonic concentrations (i.e., about 0.9 weight percent) of sodium chloride, although concentrations about 0.2 to about 2 weight percent are useful.

[0027] Optionally, the formulations will contain a pH buffer, to maintain the formulation pH between about 3 and about 7. It has been found that stability of the drug (as measured by the absence of degradation reaction products) in suspension is improved by maintaining pH conditions below about 6. For reasons of tissue compatibility, excessively acidic products are not desired, so the pH should not be made to be below about 3. Some experimentation may be needed to qualify specific buffers for use in the invention: phosphate buffers in concentrations of 1 to 50 millimolar do not appear to adequately prevent caking of the particulates in the suspension when there is no added soluble salt.. A citrate-citric acid buffer, maintaining pH between about 4 and about 5, has been used with particularly good effect for both maintaining pH during storage and preventing any particulate caking in the absence of soluble salts.

[0028] The citrate-citric acid buffer may be present in suspension formulations at concentrations at least about 2 and up to about 50 millimolar. While the literature has some reports of cough being induced by such buffer systems, this seems to occur primarily at the 150-200 millimolar level, although one report attributed cough to only a 35 millimolar concentration.

[0029] Sterility or adequate antimicrobial preservation of the final packaged formulation is needed for patient protection. The use of antimicrobial preservatives is less desirable, since certain of these have been associated with adverse clinical effects, such as bronchospasm. Alternative processes which may be considered for achieving sterility usually will not include sterilization steps for the micronized drug substance or formulation, since it has been found that the drug undergoes degradation under the influence of gamma-ray irradiation and sterilizing heat conditions. Sterilization by filtration ordinarily will not be feasible, due to the suspension nature of the formulation. Thus, it is preferred to produce the mometasone furoate monohydrate under sterile conditions, conduct the drug micronization in a sterile environment, and perform a sterile packaging operation.

[0030] Methods are known for reducing particle sizes into the micrometer range, including mechanical milling, application of ultrasonic energy and other techniques. Mechanical milling frequently generates high surface temperatures on the particles, and this is undesirable

for mometasone furoate monohydrate which tends to lose some part of its hydration under the influence of high temperatures. Ultrasonic techniques are quite slow in their action, generally requiring very long processing times, but are capable of producing acceptable suspensions.

[0031] Suspensions of drug particles can rapidly undergo particulate size reduction when subjected to "jet milling" (high pressure particle in liquid milling) techniques. A presently preferred jet milling procedure for producing the formulations of the invention involves the use of the "Microfluidizer" system sold by Microfluidics International Corporation of Newton, Massachusetts, U. S.A. This device divides a fluid stream, flowing under high pressures (up to about 40,000 pounds per square inch, or 2.76×10^8 newton/meter^2), between two separate microchannel paths and then recombines them from generally perpendicular directions to create very high shear, impact and cavitation forces. By continuously recirculating suspensions through the system for a predetermined time period, it is possible to reproducibly create desired distributions of micron- and submicron-sized particles. Since the particles are always completely surrounded by liquid, their surfaces will not develop high temperatures under the influence of the size reduction forces, and the hydration water in the drug crystals will remain intact. Other useful equipment which utilizes related technology is available from Avestin Inc., Ottawa, Ontario, Canada.

[0032] The following examples are provided to further illustrate and explain certain aspects of the invention, and are not intended to limit the scope of the invention, as defined by the appended claims, in any manner.

EXAMPLE 1

[0033] Sterile mometasone furoate monohydrate is prepared by a procedure including the following steps:

(1) charge 250 grams mometasone furoate to a dissolution vessel containing 4250 mit of acetone, and mix to form a clear solution;
(2) pump the solution through a sterilizing filter, such as a filtration medium having pores not exceeding 0.2 µm in diameter, into a sterile precipitation vessel equipped with means for stirring and means for heating the contents (note that sterile equipment and a sterile environment must be used for all subsequent steps);
(3) heat the sterile solution to about 45-50°C and slowly add, over about 15 minutes, 1000 mL of sterile purified water while maintaining the temperature;
(4) while maintaining the elevated temperature, slowly add an additional 750 mL of the water, with stirring over about 30 minutes;
(5) continue the stirring and maintain the temperature for an additional 30 minutes, during which a precipitate will begin to form;
(6) slowly add an additional 5250 mL of the water over about 60 minutes, while maintaining a rapid stirring and the elevated temperature;
(7) continue stirring at the elevated temperature for about 60 minutes;
(8) cool the mixture to ambient temperature, with continued stirring;
(9) filter the precipitate (mometasone furoate monohydrate) and wash it with two 500 mL portions of the sterile purified water; and
(10) dry in a vacuum oven at 30-35°C for 12-24 hours.

[0034] The dried sterile mometasone furoate monohydrate product should have a water content, as measured by a standard Karl Fischer titration, of 3.3 percent by weight and contains 96.7 percent by weight mometasone furoate.

EXAMPLE 2

[0035] A 40 liter batch of a sterile aqueous suspension of mometasone furoate monohydrate is prepared using the following procedure:

(1) sequentially charge 2.0 grams of Polysorbate 80, 7.24 grams of citric acid monohydrate and 13.4 grams of sodium citrate dihydrate to about 1000 grams of purified water in a vessel equipped for stirring, stir to form a solution having a pH of 4.5 ± 0.5, add additional purified water to make 1315 grams of solution and filter the solution under pressure through a 0.2 µm sterilizing filter into a sterile recirculation vessel, equipped for stirring;
(2) add 360 grams of sodium chloride to about 1800 grams of purified water, stir to dissolve, add additional purified water to make 2000 grams of solution and filter under pressure through a 0.2 µm sterilizing filter into a sterile vessel;
(3) add 21.73 grams of mometasone furoate monohydrate, prepared as in Example 1, to the sterile solution of step (1) and commence stirring the vessel contents to form a suspension;
(4) pass the mixture of the preceding step through a sterilized Model 210B-EH pilot-scale Microfluidizer operating at 17500 ± 500 pounds per square inch (1.21×10^8 newton/meter^2 ± 3.45×10^6 newton/meter^2) gauge pressure for 40 ± 5 minutes while returning the Microfluidizer discharge into the stirred recirculation vessel;
(5) transfer the micronized mometasone furoate suspension from the recirculation vessel to the vessel of step (2);
(6) rinse the Microfluidizer with sterile purified water and add the rinse water to the suspension formed in the preceding step, then add a sufficient additional quantity of the water to form a suspension weighing 40100 grams; and

(7) fill individual sterile containers with a desired amount of suspension (containing 0.5 mg of mometasone furoate per milliliter and having a specific gravity of 1.003 g/cm^3) for use in a nebulizer.

[0036] The weight for the mometasone furoate monohydrate includes a 5 percent overcharge to compensate for manufacturing losses.

EXAMPLE 3

[0037] Using the procedure of the preceding example, a suspension is prepared which has the following composition and a pH about 4.5:

Mometasone furoate*	500 µg
Polysorbate 80	50 µg
Citric acid monohydrate	181 µg
Sodium citrate dihydrate	335 µg
Sodium chloride	9 mg
Water for injection, USP	to make 1 mL

* From mometasone furoate monohydrate

[0038] A particle size distribution is determined for the suspension by a laser light scattering technique. A Malvern 2600 instrument, manufactured by Malvern Instruments, Malvern, Worcestershire, United Kingdom, is set up with a liquid flow cell and a 63 mm lens, and operated in its "particle in liquid" mode with water (containing a small amount of Polysorbate 80 as a wetting agent) as the vehicle. Drug suspension is added until an optimum light obscuration is achieved, then the measurements are obtained. Data are calculated and expressed on a volume distribution basis, and are graphically represented as shown in Fig. 1. This suspension has a median particle size of 1.24 µm and a mean particle size of 1.34 µm.

EXAMPLE 4

[0039] Commercially available nebulizers are used to determine the drug delivery characteristics for the suspension of the preceding example and two commercial suspension products: BECOTIDE beclomethasone dipropionate suspension (Glaxo) and PULMICORT budesonide suspension (Astra). The nebulizers are WHISPER JET (Marquest Medical Products, Englewood, Colorado, U.S.A.) and PARI JET (PARI Respiratory Equipment, Inc., Richmond, Virginia, U.S.A.). Suspensions are placed into the nebulizers in 3 mL amounts, and the equipment is connected to a compressor and operated according to the manufacturers' instructions. Nebulized drug is directed into the top of a 500 mL separatory funnel containing a 1 gram plug of cotton, and the lower outlet of the funnel is connected to a vacuum line. After the nebulizer becomes dry, the vacuum line is disconnected and the funnel (with the plug) is washed with 25 mL of a solvent for the drug (e. g., methanol), which is then collected and analyzed for the drug by high performance liquid chromatography to determine the percentage of originally charged drug which was delivered to the funnel.

[0040] Results are obtained as follows, where the values are averages of four determinations:

	Percent Delivered	
Product	Pari Jet	Whisper Jet
Example 3	32.9	23.6
Becotide	23.5	13.4
Pulmicort	31.9	18.1

EXAMPLE 5

[0041] As in preceding Example 3, the following suspension formulations are prepared, each containing sufficient sterile water to make a final volume of 1 mL:

Formula	5A	5B	5C
Mometasone furoate, µg	250	500	500
Polysorbate 80, µg	50	500	50
Citric acid monohydrate, µg	181	181	80
Sodium Citrate dihydrate, µg	335	335	470
Sodium chloride, mg	9	9	9

[0042] The mometasone furoate content is provided by mometasone furoate monohydrate.

EXAMPLE 6

[0043] As in preceding Example 3, the following suspension formulations are prepared, each containing sufficient sterile water to make a final volume of 1 mL:

Formula	6A	6B	6C
Mometasone furoate, µg	500	500	750
Polysorbate 80, µg	50	50	50
Citric acid monohydrate, µg	294	181	181
Sodium Citrate dihydrate, µg	174	335	335
Sodium chloride, mg	9	4.5	18

[0044] The mometasone furoate content is provided by mometasone furoate monohydrate.

Claims

1. A nebulizer suspension comprising water, mometasone furoate monohydrate, a nonionic surfactant, sodium chloride or potassium chloride, and optionally a pH buffer.

2. A suspension according to Claim 1, wherein the suspension consists essentially of water, mometasone furoate monohydrate, a nonionic surfactant, sodium chloride or potassium chloride, and optionally a pH buffer.

3. The suspension of Claim 1 or 2, containing mometasone furoate monohydrate at a concentration of 50 micrograms to 5 milligrams, per milliliter of suspension.

4. The suspension of any preceding claim, wherein the surfactant comprises a Polysorbate surfactant.

5. The suspension according to Claim 4, wherein the surfactant comprises Polysorbate 80.

6. The suspension of any of Claims 1-3, wherein the surfactant comprises a Poloxamer surfactant.

7. The suspension according to Claim 1, containing surfactant at a concentration of 50 micrograms to 1 milligram, per milliliter of suspension.

8. The suspension according to Claim 1, wherein the salt comprises sodium chloride.

9. The suspension according to Claim 1, which includes a pH buffer.

10. The suspension of Claim 9, wherein the buffer comprises a citric acid-citrate buffer.

11. The suspension of Claim 9, wherein the buffer maintains aqueous phase pH values of 3 to 7.

12. The suspension of Claim 9, wherein the buffer maintains aqueous phase pH values of 3 to 6.

13. The suspension of Claim 9, wherein the buffer maintains aqueous phase pH values of 4 to 5.

14. The suspension of any preceding claim, having a solid particles component wherein said solid particles have average sizes less than 5μm.

15. The suspension of any of Claims 1-13, having a solid particles component wherein said solid particles have average sizes less than 2μm.

16. A process for producing a nebulizer suspension, comprising combining water, mometasone furoate monohydrate, a nonionic surfactant, sodium chloride or potassium chloride, and optionally a pH buffer, and subjecting the combination to particle size reduction by ultrasonication or by jet milling.

17. A process according to Claim 16, comprising combining ingredients consisting essentially of water, mometasone furoate monohydrate, a nonionic surfactant, sodium chloride or potassium chloride, and optionally a pH buffer, and subjecting the combination to particle size reduction by ultrasonication or by jet milling.

18. The process of Claim 16, wherein the combination includes a pH buffer.

19. The process of any of Claim 16, wherein particle size reduction is continued to produce solid particles having sizes less than 10μm, preferably less than 5μm.

20. The process of any of Claim 16, wherein particle size reduction is continued to produce solid particles having average sizes less than 2μm.

21. Use of a suspension according to any of claims 1-15 in manufacture of a medicament for treatment of airway disorders by nebulization to surfaces of the airway.

22. Use of a suspension prepared by a process according to any of claims 16-20 in manufacture of a medicament for treatment of airway disorders by nebulization to surfaces of the airway.

Patentansprüche

1. Zerstäuber-Suspension, umfassend Wasser, Mometasonfuroat-Monohydrat, ein nicht-ionisches Tensid, Natriumchlorid oder Kaliumchlorid und gegebenenfalls einen pH-Puffer.

2. Suspension nach Anspruch 1, **dadurch gekennzeichnet, dass** die Suspension im Wesentlichen aus Wasser, Mometasonfuroat-Monohydrat, einem nicht-ionischen Tensid, Natriumchlorid oder Kaliumchlorid und gegebenenfalls einem pH-Puffer besteht.

3. Suspension nach Anspruch 1 oder 2, die Mometasonfuroat-Monohydrat in einer Konzentration von 50 μg bis 5 mg pro ml der Suspension enthält.

4. Suspension nach einem der vorstehenden Ansprüche, **dadurch gekennzeichnet, dass** das Tensid ein Polysorbat-Tensid umfasst.

5. Suspension nach Anspruch 4, **dadurch gekennzeichnet, dass** das Tensid Polysorbat 80 umfasst.

6. Suspension nach einem der Ansprüche 1-3, **dadurch gekennzeichnet, dass** das Tensid ein Poloxamer-Tensid umfasst.

7. Suspension nach Anspruch 1, die ein Tensid in einer Konzentration von 50 µg bis 1 mg pro ml Suspension enthält.

8. Suspension nach Anspruch 1, **dadurch gekennzeichnet, dass** das Salz Natriumchlorid umfasst.

9. Suspension nach Anspruch 1, die einen pH-Puffer umfasst.

10. Suspension nach Anspruch 9, **dadurch gekennzeichnet, dass** der Puffer einen Zitronensäure-Citrat-Puffer umfasst.

11. Suspension nach Anspruch 9, **dadurch gekennzeichnet, dass** der Puffer pH-Werte der wässrigen Phase von 3 bis 7 beibehält.

12. Suspension nach Anspruch 9, **dadurch gekennzeichnet, dass** der Puffer pH-Werte der wässrigen Phase von 3 bis 6 beibehält.

13. Suspension nach Anspruch 9, **dadurch gekennzeichnet, dass** der Puffer pH-Werte der wässrigen Phase von 4 bis 5 beibehält.

14. Suspension nach einem der vorstehenden Ansprüche, die eine Komponente von festen Partikeln aufweist, wobei die besagten festen Partikel durchschnittliche Größen von weniger als 5 µm aufweisen.

15. Suspension nach einem der Ansprüche 1-13, die eine Komponente von festen Partikeln aufweist, wobei die besagten festen Partikel durchschnittliche Größen von weniger als 2 µm aufweisen.

16. Verfahren zur Herstellung einer Zerstäuber-Suspension, Schritte umfassend, bei denen man Wasser, Mometasonfuroatmonohydrat, ein nicht-ionisches Tensid, Natriumchlorid oder Kaliumchlorid und gegebenenfalls einen pH-Puffer vereinigt, und die Zusammensetzung einer Reduzierung der Partikelgröße durch Behandlung mit Ultraschall oder einer Strahlmühle unterwirft.

17. Verfahren nach Anspruch 16, Schritte umfassend, bei denen man Bestandteile vereinigt, die im Wesentlichen aus Wasser, Mometasonfuroat-Monohydrat, einem nicht-ionischen Tensid, Natriumchlorid oder Kaliumchlorid und gegebenenfalls einem pH-Puffer bestehen, und die Zusammensetzung einer Reduzierung der Partikelgröße durch Behandlung mit Ultraschall oder einer Strahlmühle unterwirft.

18. Verfahren nach Anspruch 16, **dadurch gekennzeichnet, dass** die Zusammensetzung einen pH-Puffer enthält.

19. Verfahren nach Anspruch 16, **dadurch gekennzeichnet, dass** die Reduzierung der Partikelgröße fortgesetzt wird, um feste Partikel mit Größen von weniger als 10 µm, vorzugsweise weniger als 5 µm herzustellen.

20. Verfahren nach Anspruch 16, **dadurch gekennzeichnet, dass** die Reduzierung der Partikelgröße fortgesetzt wird, um feste Partikel mit durchschnittlichen Größen von weniger als 2 µm herzustellen.

21. Verwendung einer Suspension nach einem der Ansprüche 1-15 zur Herstellung eines Medikamentes zur Behandlung von Atemwegs-Erkrankungen durch Zerstäubung auf Oberflächen der Atemwege.

22. Verwendung einer Suspension, die durch ein Verfahren nach einem der Ansprüche 16-20 hergestellt wurde, zur Herstellung eines Medikamentes zur Behandlung von Atemwegs-Erkrankungen durch Zerstäubung auf Oberflächen der Atemwege.

Revendications

1. Suspension de nébuliseur comprenant de l'eau, du furoate de mométasone monohydraté, un surfactant non ionique, du chlorure de sodium ou du chlorure de potassium, et en option un tampon de pH.

2. Suspension selon la revendication 1, dans laquelle la suspension consiste principalement en eau, furoate de mométasone monohydraté, surfactant non ionique, chlorure de sodium ou chlorure de potassium, et en option un tampon de pH.

3. Suspension selon la revendication 1 ou 2, contenant du furoate de mométasone monohydraté à une concentration de 50 microgrammes à 5 milligrammes, par millilitre de suspension.

4. Suspension selon n'importe laquelle des revendications précédentes, dans laquelle le surfactant est composé d'un Polysorbate surfactant.

5. Suspension selon la revendication 4, dans laquelle le surfactant est composé de Polysorbate 80.

6. Suspension selon n'importe laquelle des revendications 1 à 3, dans laquelle le surfactant est composé d'un Poloxamer surfactant.

7. Suspension selon la revendication 1, contenant un surfactant à une concentration de 50 microgrammes à 1 milligramme, par millilitre de suspension.

8. Suspension selon la revendication 1, dans laquelle le sel est composé de chlorure de sodium.

9. Suspension selon la revendication 1, qui comprend un tampon de pH.

10. Suspension selon la revendication 9, dans laquelle le tampon est composé d'un tampon acide citrique-citrate.

11. Suspension selon la revendication 9, dans laquelle le tampon maintient la valeur du pH de la phase aqueuse entre 3 et 7.

12. Suspension selon la revendication 9, dans laquelle le tampon maintient la valeur du pH de la phase aqueuse entre 3 et 6.

13. Suspension selon la revendication 9, dans laquelle le tampon maintient la valeur du pH de la phase aqueuse entre 4 et 5.

14. Suspension selon n'importe laquelle des revendications précédentes, ayant un composant sous forme de particules solides dans lequel lesdites particules ont des tailles moyennes inférieures à 5µm.

15. Suspension selon les revendications 1 à 13, ayant un composant sous forme de particules solides dans lesdites particules ont des tailles moyennes inférieures à 2µm.

16. Procédé pour produire une suspension de nébuliseur, composé d'une combinaison d'eau, de furoate de mométasone monohydraté, d'un surfactant non ionique, de chlorure de sodium ou de chlorure de potassium, et en option d'un tampon de pH, et selon la combinaison de la réduction de la taille des particules par un moyen ultrasonique ou par broyage à jet.

17. Procédé selon la revendication 16, comprenant une combinaison de substances consistant principalement d'eau, de furoate de mométasone monohydraté, d'un surfactant non ionique, de chlorure de sodium ou de chlorure de potassium, et en option d'un tampon de pH, et selon la combinaison de la réduction de la taille des particules par un moyen ultrasonique ou par broyage à jet.

18. Procédé selon la revendication 16, dans lequel la combinaison comprend un tampon de pH.

19. N'importe quel procédé selon la revendication 16, dans lequel la réduction de la taille de particule est continuée pour produire des particules solides ayant des tailles inférieures à 10µm, préférablement inférieures à 5µm.

20. N'importe quel procédé de la revendication 16, dans lequel la réduction de la taille de particule est continuée pour produire des particules ayant des tailles inférieures à 2µm.

21. Utilisation d'une suspension selon n'importe laquelle des revendications 1 à 15 dans la fabrication d'un médicament pour le traitement des troubles des voies aériennes par nébulisation des surfaces des voies aériennes.

22. Utilisation d'une suspension préparée par un procédé selon n'importe laquelle des revendications 16 à 20 dans la fabrication d'un médicament pour le traitement des troubles des voies aériennes par nébulisation des surfaces des voies aériennes.